

American Pediatric Society John Howland Award 1999

Presentation to Abraham Morris Rudolph, MD¹

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President Kaback, previous Howland Award recipients, Rhona, Abe, members of the Rudolph clan, APS members, and guests. It is with considerable pride and the greatest of personal pleasure that I introduce to you the recipient of this year's John Howland Award of the American Pediatric Society, Abraham Morris Rudolph. Through his tireless efforts and unwavering commitment to excellence, his extraordinary research creativity, his clinical skill and acumen, his inspiring teaching, his clear and direct communication, his exemplary leadership, and his kind and gentle humanity, Abe Rudolph has changed the face of Pediatric Cardiology and of Pediatric Medicine over a span of time which now approaches 50 years.

Abe Rudolph was born in South Africa on February 3, 1924. The family lived modestly on the proceeds of a general store that was owned by Abe's father. As a child, many of the personality traits that were to become so characteristic of Abe were not yet evident. While the Abe that most of us have come to know and admire is refined, humble, and always in command of the moment, Abe Rudolph in those early years was known as the scourge of the neighborhood. He was mischievous and something of a troublemaker. There were, however, glimmerings of what was to come. For example, he demonstrated early on the manual dexterity that was later to become so highly evolved in the catheterization laboratory. Once he boasted to a friend that he could open the front door to his father's store with nothing more than the key to a sardine can. Under the cover of darkness, the two of them stole over to the Rudolph emporium where Abe inserted the sliver of metal into the lock, and without the benefit of a guide wire or fluoroscopy began to manipulate the tumblers. He turned the knob, pushed on the door, and it swung open. The unexpected success so terrified our hero and his accomplice that they left the door widely ajar, turned around, and fled as rapidly as possible. It wasn't until much later that they learned that Abe's uncle, who closed the store in the evenings frequently forgot to secure the lock. Always eager to turn adversity to advantage, Abe soon recovered from this trauma and the next day penned an account of his adventure. Those in the audience who have served on various award committees that have honored Abe over the

The 1991 "Abey" Awards



Figure 1. The Abey Award.

years may recall that the first paper on his CV is entitled "Transkeylock Septostomy of the Central Portal."

Other Rudolph characteristics that were evident in those early years were a certain wanderlust and a clear desire to be the center of attention. I am told by Rhona that at the age of six, Abe ran away from home one morning and stole off to a nearby park where he waited for the search party which never arrived. Late that night, he went home, climbed through a window, and went to bed. His family was apparently entirely oblivious to his absence, which was a significant blow to his ego. From this experience he learned the importance of obtaining adequate recognition for one's efforts through suitable communication

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and public relations. As Napoleon said, "Glory is fleeting, but obscurity is forever." Those early years were good ones for Abe and his brothers, Jack and Nate. While one can argue about the relative contributions of genetics and environment, there was clearly something quite extraordinary about this sibship as all three of the brothers Rudolph were high academic achievers, and all three went on to great success in their respective careers.

Things came fairly easy for Abe, or at least he made it appear to be so. He had great academic success at the University of Witwatersrand, where he not only stood first in his class, but he established himself as the first student to graduate with a perfect record on all examinations. This distinction was not to last unchallenged for too great a time, however, as the following year, a student named Julien Hoffman equaled this accomplishment. Following postgraduate training at Johannesburg General Hospital and the Transvaal Memorial Hospital for Children, Abe decided to seek his fortune in the United States. Abe's strong reaction to the socioeconomic inequities and political repression of South Africa in the early 1950s as well as a recognition of the more substantial academic opportunities in Boston caused him to matriculate to the Children's Hospital in 1951. He was not to return to South Africa for many years. Abe's first appointment in Boston was as an *unpaid* fellow in the Division of Hematology. I understand from Phil Pizzo that this is still characteristic of the financial arrangements surrounding most fellowship appointments at Children's Hospital. Shortly after arriving in Boston, however, Abe learned that there was an unusual *funded* position to work with Alex Nadas in the nascent field of Pediatric Cardiology. Faced with the conflict between principle and pragmatism, our hero went for the cash. For Abe Rudolph as for the well known novelist James Baldwin, "Money it turned out, was exactly like sex. You thought of nothing else if you didn't have it and thought of other things if you did." Abe was now free to think about other things. He was also cognizant of the advice of Spike Milligan who said "Money can't buy friends, but you get a better class of enemy."

Abe remained at Harvard for 9 years. His survival and success in this supercompetitive environment was the result of a unique philosophy that Abe adopted early on in his days in New England.... "Dress British. Think Yiddish."His first publication from this era was entitled, "The Use of Digitalis in Infants and Children," and appeared in the *New England Journal of Medicine*. But Abe's greatest accomplishments related to his perfecting the techniques that enabled the safe and informative catheterization of the hearts of infants and children with congenital heart disease and the elegant characterization of the physiology attendant to many lesions. With colleagues like Julien Hoffman (who followed Abe to Boston), Peter Auld, Jackie Noonan, the irrepressible Hungarian Nadas, and Robert Gross, they described the hemodynamics of patent ductus arteriosus, ventricular septal defect, atrial septal defect, pulmonic stenosis with or without an intact ventricular septum, critical aortic stenosis, and transposition of the great vessels. With Nadas and Clem Smith, Abe published a classical paper on the circulation in the respiratory distress syndrome. He also began studies that were to occupy much of his career on the

regulation of the pulmonary circulation including the first description of primary pulmonary hypertension as well as the effects of tolazoline in providing some relief for this syndrome. Again in a manner that would portend much, Abe carried out parallel studies in the dog lab, which allowed him to explore the role of serotonin in regulating pulmonary vascular resistance. One must remember how primitive the tools available were at that time. Image intensification had not yet made fluoroscopy facile; pressure transducers were large and had a delayed response time; catheters had to be custom made and so on. Abe's abilities to successfully study infants with these methods were the envy of many and so a steady stream of visitors came to the catheterization laboratories in Boston to learn these methods and in turn Abe was invited to travel to other countries to teach these techniques, which he often generously agreed to do.

In 1960, Abe accepted the position of Director of the Division of Pediatric Cardiology at the Albert Einstein College of Medicine. During the ensuing 5 years, he developed a program of considerable strength and published important insights into the pathophysiology of cardiac disease in childhood. There was a 1963 *JCI* paper on "The Mechanism of Pulsus Paradoxus During Acute Pericardial Tamponade," a paper the same year in *Pediatrics* describing the occurrence of lactic acidosis in children with severe cyanotic congenital heart disease, a publication in the *Journal of Pediatrics* describing the diagnosis of "Anomalous Left Coronary Artery Arising from the Pulmonary Artery with a Large Left-to-right Shunt in Infancy," and a treatise on "The Hemodynamics of Congenital Heart Block." While these continued to be highly productive years, there were rumblings in the West.

UCSF in the mid-1960s was viewed by most as a reasonably solid regional medical school that had strong clinical programs and a small Pediatric program that trained capable general pediatricians and a few good specialists. However, a few years before, Julius Comroe had been recruited from Philadelphia to establish the Cardiovascular Research Institute. The CVRI's first fellow was a pediatrician named Bill Tooley, who established the newborn intensive care unit at UCSF. Bill worked closely with John Clements, who was studying a wonderful new substance called surfactant. Holly Smith was recruited as the Chair of the Department of Medicine, and he in turn helped to recruit Bill Rutter as Chair of Biochemistry. Rutter was later to distinguish himself by being the first to clone the insulin gene and the hepatitis C genome and later established the Chiron Corporation. Holly also helped to recruit the 1997 Howland award recipient, Mel Grumbach, as Chair of Pediatrics. Some in the audience who have visited the Departmental offices at UCSF will know that they have a somewhat cluttered appearance. This is because we never throw anything away. At times like this, I am grateful as I have been able to locate some original correspondence that allows a unique insight into history. Before Mel Grumbach arrived in San Francisco, the previous Chairman, Ed Shaw, had established a search committee to identify a Professor of Pediatric Cardiology consisting of Comroe, Clements, and Tooley, and they identified Abe as the most outstanding candidate. Comroe wrote, "Wherever I have been in the United States or in foreign countries, Dr.

Abraham Rudolph is always listed as the #1 pediatric cardiologist. To my mind, Dr. Rudolph is the ideal University professor in that he does highly original and exciting research, has a deep interest in teaching at all levels, and is absolutely superb as a clinician." Alex Nadas wrote, "I have known Dr. Rudolph for over 15 years. I watched him grow, develop, and reach full maturity. Unquestionably, he is today *the* outstanding investigator in Pediatric Cardiology in the United States. In addition, he is a superb clinician as well as a good teacher." After securing the approval of the Chair designate Grumbach (Mel was always a risk taker), Abe was offered the position and fortunately saw the opportunities of this rich new land on the shores of the Pacific.

Actually, Abe was the stealth vanguard of a South African invasion of San Francisco, for soon after Abe came Hoffman, Heymann, and Silverman. I am told that recently one of the current Cardiology fellows and the most recent South African expat, Wayne Tworetzky answered the phone at extension 1373. Recognizing the characteristic accent, the voice at the other end enquired ..Abe? No said Wayne....Julien? No... Michael.....No.....Norman.....No. Well I give up. Click.

Abe developed an intense interest in the fetal circulation and the remarkable physiologic changes that occur at and shortly after birth. With a talented succession of collaborators, Abe was able to create progressively more sophisticated preparations such as the chronically catheterized fetal sheep that would yield new insights. When methods needed to answer questions didn't exist, he invented them (such as the use of radioactive microspheres for the measurement of regional blood flow). In spite of his well-known tremor, he was able to catheterize the smallest of fetal vessels. I believe that in a few minutes you will hear from Abe about his most recent studies that require the catheterization of fetal coronary arteries. Another of Abe's great native talents is his ability to visualize three dimensional anatomy. Several former trainees tell of the experience of encountering difficulties in passing a catheter into the position required and calling Abe in his office for advice. After they described what they saw on the video screen, Abe would say something like "withdraw the catheter 3 cm, rotate it clockwise 270 degrees, advance it 4 cm, rotate counterclockwise 45 degrees, and advance it until you see the pressure tracing change." Invariably the instructions provided would work. This may represent one of the earliest examples of telemedicine. In summation, Abe is a perfectionist, but he has always been eager to share his technical expertise at every opportunity.

Abe is a gifted and passionate teacher at all levels....fellows, residents, and students. Norman Silverman has said that when Abe used to run the clinical conference regarding the patients to be catheterized the next day, there was often a far away look in his eyes. Later they found out he was not deep in thought, but just looking at the traffic on the Bay Bridge and contemplating his drive back to Berkeley. Conference usually concluded when the major traffic jam had ended. It was at those conferences, however, that many of them found out how it was possible for Abe to magically make you forget - even your name when he asked, "Well, how will you approach this catheterization tomorrow?"

Many mysteries of fetal physiology would come to be revealed through the extraordinary work in the sheep labs at UCSF. More than 300 papers would be published, the most recent of which appeared just last month in *Pediatric Research*. Among the many practical results of these investigations would be the development of the techniques to make possible the first successful fetal surgery in humans by Michael Harrison and his colleagues. Also of considerable note are the classic studies published with Michael Heymann, which elucidated the role of prostaglandins in the constriction of the ductus arteriosus, the ability of prostaglandin synthase inhibitors to close a patent ductus nonsurgically and the use of prostaglandin infusion to maintain the ductus in an open state in infants who have ductal dependant congenital heart lesions. These procedures, which had their beginnings in the sheep lab, were extended to clinical practice and have been used worldwide to save the lives of countless infants.

Abe has been a prolific writer. In addition to his many scientific publications, Abe is responsible for a classic textbook entitled "Congenital Diseases of the Heart-Physiologic Considerations in Diagnosis and Management." To the aficionados, this is known as the red book, and it was published at about the same time as the other red book of Chairman Mao. In addition Abe has edited the 16th through 20th editions of the Appelton textbook, "Pediatrics." The 20th edition, which was published in 1996, was co-edited with Julien Hoffman and Abe's son, Colin. Given Julien's extraordinarily long and filial association with Abe, I think that this may qualify as the family textbook.

I think that Abe would agree that the greatest legacy of his 33 years at UCSF is found in the over 100 fellows he has trained and who have gone on to considerable distinction. They are Deans, Department Chairpersons, and Division Directors, and some have even worked for a living. Together, they have changed our knowledge of development, physiology, and the way in which infants with heart disease can be treated. Abe would probably be the first to agree that in addition to the satisfaction that the accomplishments of his trainees have brought, he has received many other rewards and honors. He has even had awards named after him (Fig. 1).

Among the many awards that Abe did receive are the E. Mead Johnson Award in Research and the Borden Research Award; and he was selected to be the faculty lecturer at UCSF, the highest award that the faculty at UC can bestow on one of their own members. Abe has also been the recipient of the lifetime Achievement in Teaching Award of the American Academy of Pediatrics, the Research Achievement Award of the American Heart Association, and the Joseph W. St. Geme Leadership Award. He has served as the President of this Society, has been elected to the Institute of Medicine, and has been recognized internationally with the Arvo Yllopo Medal from Finland, the J.H.P. Jonxis Medal from the Netherlands, and an honorary degree from the University of Paris; he also received the 75th Jubilee Medal from his alma mater, the University of Witwatersrand. Lest all of this go to your head, however, Abe, I need to remind you of the sad truth about academic life...by the time you've made it, you've had it.

In 1986, Abe assumed the Chairmanship of the Department of Pediatrics and held that post with distinction for 5 years. As

my immediate predecessor, I know better than most, how hard he worked and how skillful he was in developing the Department. As you might expect, Abe was particularly devoted to the residents and they were very fond of him. When he stepped down from the Chair, a fund was established to create the Rudolph resident's lounge as an appropriate way to thank Abe for these years of service. Subsequently, with characteristic grace, he has been a source of wise counsel to me, but has never been critical of the many mistakes that I have made and which he likely could have avoided.

It would be impossible to complete a description of Abe Rudolph without saying something about Rhona, their children, and grandchildren. Abe and Rhona were truly childhood sweethearts and have been blessed to share a lifetime together (Fig. 2). It would be hard to find a couple more devoted and supportive of one another. Abe has also been a loving father to Linda, Jeff, and Colin. Growing up in an active, busy household was a defining experience for both the children and for Abe. The kids learned to expect to see sheep, pigs, and dogs that were the subjects of experiments as houseguests from time to time. In turn, he became addicted to working in front of the television and in fact, to this day, he cannot work in a silent environment. By the way, his favorite TV shows are MASH, Mission Impossible, and Hawaii Five-O. Abe is absolutely captivated by his grandchildren and they are simply infatuated with him. It reminds one of the old adage that the reason that children and their grandparents are so close to one another...is that they share a common enemy.

Abe has many friends the world over. He has been active in political causes, speaks out whenever he sees a wrong that needs addressing, and truly has a concern for his fellow man. Abe is well read, knowledgeable about music, a gardener of great skill, and an enophile of wide repute. An evening's conversation with Abe is always a sheer delight. Most of all, he has a kind and gentle nature and an exceptional generosity of spirit, which has endeared him to so many.

Abe, on behalf of the American Pediatric Society, we congratulate you on your many achievements. By honoring you, we truly do honor to the Society. Your leadership and unflag-



Figure 2. Abe and Rhona at their Sonoma home.

ging commitment to excellence has been of the very best kind...by example. You have taught us all how to work in an atmosphere of mutual respect and to strive to reach the highest levels that we can. You have done all of this with style, with grace, and with class. It is my honor to ask you to come forward and to receive the Howland Award.

Acceptance

ABRAHAM M. RUDOLPH

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Dr. Kabach, members of the Academic Pediatric Societies and guests, I am truly appreciative of this singular honor. And to Larry Shapiro, thank you for that magnanimous introduction.

It is now part of tradition that the awardee mentions individuals who have had an impact on his or her development. Certainly many have contributed to mine, but I have time today to acknowledge only those who have had a major role in molding my life and my career. First and foremost in influencing my life has been my wife Rhona. We will be celebrating our 50th anniversary later this year. She has been my most ardent supporter, as well as my most constructive critic. Our children and grandchildren have been a constant

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source of pleasure and pride. They have perhaps had more influence in molding our philosophies and attitudes than we have had on theirs.

I have had the good fortune to work with many wonderful people during my career. Alex Nadas launched me into the Pediatric Cardiology field at Children's Hospital, Boston; Cliff Barger introduced me to animal research in the Physiology Department at Harvard. The Chairmen I have served under, Henry Barnett at Albert Einstein, Mel Grumbach, and recently, Larry Shapiro at the University of California San Francisco, have all provided enthusiastic support with little interference—the best attributes a Chairman can have. I have benefited greatly from the longstanding associations with my colleagues in Pediatric Cardiology. My association with Julien Hoffman dates to 1961, with Michael Heymann to 1965, with Paul Stanger to 1967, with Norman Silverman to 1972, with David Teitel to 1980, and with James Bristow to 1982. They all started as Fellows in my program and each has achieved international recognition. Relative newcomers are George van Hare, Michael Brook, and Philip Moore, with whom the association has been only about 10 years.

I have also been privileged to have the outstanding administrative support of Muriel Byram, Suzanne Gottschalk, and Pat Hunter. Many of my contributions have been made in research in fetal physiology. Over the past 30 y, I have been extremely fortunate that Chris Roman has been my research associate in our sheep facility. She has been instrumental in helping to develop many of the experimental models we have used so effectively in our laboratory.

Twenty-five years ago, I was in Beijing (then Peking). The Chinese Medical Association extended an invitation to six adult cardiologists and me to tour China. The wording of the invitation was amusing to us at the time, because we were being invited to teach and learn. In retrospect, I believe that the phrase

To Teach and Learn

expresses the relationship that should exist between mentor and student. I certainly have gained immensely from the students, residents, fellows, and visiting scholars who have trained with me, and I am grateful for what I have learned from them.

Certain individuals have a unique impact because what they say or do creates a long-lasting impression. I would like to mention three of these people and indicate how they have profoundly influenced my attitudes and behavior. Julius Comroe was Director of the Cardiovascular Research Institute at the University of California, San Francisco. A wise man and dedicated educator—I use the term educator because he introduced many innovative approaches to teaching—he taught me that perhaps *the* most important responsibility of an academician is the nurturing and education of young individuals. Sam Javett was an astute Attending Pediatrician when I was a resident at the Children's Hospital in Johannesburg, South Africa. One of his favorite quotes was: "Do not model yourself after orthopedists. They have their brains encased in plaster of paris."

This has stimulated me to try to adhere to certain principles: To try to keep one's mind open in approaches to diagnosis and therapy, as well as in conducting research; to be critical of one's own techniques, results and interpretations; and to be prepared and willing to modify one's own concepts.

The third person who had a special impact on me is Alexander Lee McGregor. He was one of the Chief Surgeons at the Johannesburg General Hospital. When I was a medical student on surgical clerkship, I made, even though I say it myself, an astute diagnosis that had not been considered by any of the faculty. He presented me with a copy of his book with the inscription shown in Fig. 1. This reads: May you continue, as you have begun, to make truth your aim in Medicine.

What did I learn from this? Well, what more can I say? This says it all.

I can only say that I have tried to live up to his expectations.

I should probably stop at this point, but, whenever I am before an audience, I feel compelled to try to make challenging and provocative comments. So today I cannot refrain from discussing a topic that has been of considerable concern to me lately, that is:

Iatrogenesis in Pediatrics

The word, iatrogenesis, is derived from the Greek, Iatrikos, meaning Physician, Genesis, creation. The term refers to problems induced by physicians. I do not intend to belabor the common problems of inappropriate drug dosage or adverse effects of technical procedures, but rather, to emphasize long-term consequences of therapy. Although most of us believe that we always do the best for our patients, this is not everybody's opinion. Voltaire had a particularly dim view of our therapeutic capabilities. He maintained that "Doctors are men that prescribe medicine of which they know little to cure disease of which they know less to human beings of which they know nothing" 1.

Today, I would like to raise concerns regarding the use of prenatal glucocorticoid therapy with the objective of maturing pulmonary function in prematurely born infants. As background to raising these concerns, I would like to present a few instances of adverse effects presenting long after an insult.

The first example is the development of thyroid carcinoma in young individuals. The association between thyroid carcinoma and irradiation of the thymus was first suggested by Duffy in 1950 2. In 1964, 528 instances of thyroid cancer were reported, occurring 3–30 y after irradiation to the neck of infants and children for benign conditions such as "thymic enlargement," enlarged tonsils and adenoids, and facial acne 3.

Another example, which was perhaps even more difficult to recognize because it occurred many years after prenatal therapy, is the development of vaginal adenocarcinoma in young women whose mothers had taken diethylstilbestrol during the pregnancy. The relationship of vaginal adenocarcinoma in young women aged 14–22 y, to the administration of diethylstilbestrol to their mothers during pregnancy, was reported by Herbst *et al.* in 1971 4. The use of diethylstilbestrol was promoted by Smith and Smith in an attempt to reduce the risks of late pregnancy toxemia and premature delivery 5. The research on which the Smiths' recommendations were based was later shown to be erroneous 6. Yet thousands of women received diethylstilbestrol during late pregnancy.

The concept that an insult during fetal life may have consequences that are manifest later in adult life has recently been emphasized by Barker. He has reported an association between fetal malnutrition and occurrence of disease in adults. He stated

Mr Rudolph

May you continue as far
have begun to make truth
your aim in medicine.

Leah Suggs

Stambridge
Sept. 14 43.

that "many human fetuses have to adapt to a limited supply of nutrients and in doing so permanently change their physiology and metabolism. These "programmed" changes may be the origins of a number of diseases in later life, including coronary artery disease and the related disorders, stroke, diabetes, and hypertension" 7. This "programming" could well be the result of changes in the hormonal milieu of the fetus.

Glucocorticoids have been shown to be effective in inducing the production of lung surfactant and thus reducing the risk of respiratory distress syndrome in prematurely born infants. Normally fetal plasma glucocorticoid concentrations are lower than those in the mother because fetoplacental 11-hydroxysteroid dehydrogenase inactivates glucocorticoids. Dexamethasone and betamethasone administered to the mother cross the placenta; they are not affected by the enzyme and can thus raise fetal glucocorticoid concentrations. Glucocorticoid administration to women who have threatened abortion is now strongly recommended. A consensus statement was issued by a committee meeting under the auspices of the National Institutes of Health:

Antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal mortality and morbidity, as well as substantial savings in health care costs. The use of antenatal corticosteroids for fetal maturation is a rare example of a technology that yields substantial cost savings in addition to improving health 8.

Most follow-up studies suggest there are few adverse effects in the short term. But what about long-term effects?

Julius Comroe espoused the dictum "No drug produces only the effect for which it is prescribed. It invariably affects other functions and organ systems."

Evidence is accumulating that an increase in glucocorticoid concentrations in the fetus before the normal predelivery rise may have serious late effects. Thus fetal exposure may be associated, in the adult, with diabetes due to programming of the hepatic enzyme, phosphoenolpyruvate carboxykinase (PEPCK), and of glucocorticoid receptor expression 9. Edwards has suggested an association between a dysfunction of the placental glucocorticoid barrier and the development of hypertension in the adult 10.

As a cardiologist, my concern is that exposure of the fetus to glucocorticoids may have long-term effects in adult life because of

interference with myocardial growth patterns. Morphologically, the fetal myocardium is quite different from that of the adult. Adult myocytes are large, with diameters of 15–25 microns, whereas fetal myocytes are much smaller, with diameters of 5–7 microns (Fig. 2). Myocardial growth in the fetus is accomplished predominantly by hyperplasia (increase in cell number), whereas in the adult, it is largely achieved by hypertrophy (increase in cell size). This change in growth pattern occurs at birth. Recently, studies I have conducted in fetal lambs have indicated that cortisol has an important role in initiating this change. Normally, in the fetal lamb, plasma cortisol concentrations are low, but rise within 2–3 d before delivery 11. I propose that this surge in cortisol concentrations just before birth initiates the normal postnatal change in myocardial growth pattern.

I developed a preparation in lambs at about 120 d gestation in which cortisol could be infused for several days into the left coronary artery to achieve the high concentrations, noted just before birth, in blood perfusing the left ventricular myocardium 12. The concentrations in the general circulation and in blood perfusing the right ventricle were not affected. Normally, left ventricular myocardial DNA concentration is higher than that in the right ventricle. Because protein concentrations are the same, the protein/DNA ratio is lower in left ventricular myocardium. Cortisol perfusion of the left ventricular myocardium for 2–4 d dramatically reduced DNA concentration and increased protein/DNA ratio, without affecting protein concentration. So the effect of cortisol is to inhibit hyperplasia and to reduce the total number of myocytes.

Thus, if the myocardium is exposed to high concentrations of cortisol during fetal life, some time before term gestation, the total number of myocytes in the heart would be less than normal. To achieve the same ventricular muscle mass relative to body size with growth, individual myocytes have to be larger, *i.e.* they would have to undergo more postnatal hypertrophy than normal myocytes. An increased workload on the myocardium promotes greater hypertrophy; also damage to some myocytes will result in hypertrophy of those remaining, but the extent to which myocytes can hypertrophy is limited.

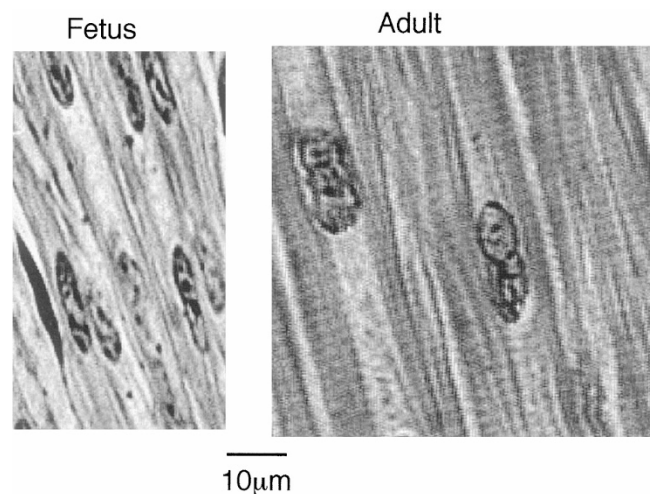


Figure 2. Left ventricular myocardium from fetal lamb (125 d gestation) and adult sheep showing small myocytes in fetus (diameter 5–7 μ) and large myocytes in adult (diameter 15–25).

If the heart has fewer myocytes at birth, the ability to respond to stress of increased demand, or to myocardial damage, may be reduced because individual myocytes have already undergone hypertrophy. It will require a long period of observation, decades rather than a few years to determine whether prenatal glucocorticoid administration may induce adult disease or influence adult cardiac performance. It should be possible to resolve this question in a shorter period in animals. I hope that I have been able, by this presentation, to stimulate interest in the exploration of these issues.

In closing, I would like to share with you a quote from Byron. I noticed it some years ago while strolling through the Gardens of the Villa Borghese in Rome.

But I have lived and have
not lived in vain:
My mind may lose its force,
My blood its fire,
And my frame perish in
conquering pain:
But there is that within me
Which shall tire
Torture and Time, and
Breathe when I expire
Byron, Child Harold IV, CXXXVIII

This expresses sentiments to which, I am sure, all of us aspire. Thank you again for this great honor.

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